Review Paper

The Effect of Antihypertensive Drugs on Erectile Function: A Proposed Management Algorithm

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The pharmacologic management of hypertension has long been implicated in the genesis of erectile dysfunction; the latter is considered the main reason of nonadherence to antihypertensive therapy. Older-generation antihypertensive drugs (central-acting, β blockers, diuretics) negatively affect erectile function, while newer-generation agents (calcium antagonists, angiotensin-converting enzyme inhibitors) seem to have neutral effects. Preliminary data with the latest drugs (angiotensin receptor blockers) point to a beneficial effect on erectile function. Phosphodiesterase-5 inhibitors, used for the treatment of erectile dysfunction, can be safely and effectively administered to hypertensive patients (even when on multiple-agent antihypertensive therapy), with a caution regarding α blockers. In the case when erectile dysfunction is considered to result from antihypertensive therapy, the treating physician may either add phosphodiesterase-5 inhibitors or substitute current treatment with angiotensin receptor blockers. (J Clin Hypertens. 2006;8:359–364)

Erectile dysfunction is currently considered a disease of vascular origin in many patients. Atherosclerotic lesions in penile arteries (as found with increasing age and in patients with diabetes, hypertension, or cardiovascular disease) may affect penile blood flow and impair erectile function. Thus, erectile dysfunction is more common in patients with manifestations of cardiovascular atherosclerotic disease. Erectile dysfunction is more frequent in patients with essential hypertension compared with normotensive subjects. However, a question has been raised as to whether the higher prevalence of erectile dysfunction in hypertensive patients is the result of hypertension per se, of antihypertensive treatment, or of a combination of both. In addition, whether erectile dysfunction results from the reduction of blood pressure and the subsequent decrease in penile blood flow or from specific effects of the various antihypertensive drugs on erectile function remains to be clarified.

One of five cases of erectile dysfunction is due to adverse drug events.[1] Antihypertensive drugs represent one of the most implicated classes. Older antihypertensive drugs (central-acting, β blockers, diuretics) have traditionally been considered to cause erectile dysfunction, while the newer ones (calcium antagonists, angiotensin-converting enzyme [ACE] inhibitors, and angiotensin receptor blockers [ARBs]) have either neutral effects or may even be beneficial with respect to sexual function.[2,3]

Patients who experience drug-induced erectile dysfunction (either real or perceived) are nonadherent to antihypertensive treatment. In several studies, a common cause for treatment discontinuation was erectile dysfunction.

Epidemiologic data suggest that a sedentary lifestyle represents a risk factor for erectile dysfunction; thus, it seems logical to assume that lifestyle modification will be of benefit. However, only minimal data are available to support this assumption.[4–7]

This article briefly reviews available data regarding the effect of the various antihypertensive drug

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classes on erectile function, addresses the concomitant use of phosphodiesterase-5 (PDE-5) inhibitors with antihypertensive agents, and comments on current guidelines regarding these issues.

According to current guidelines, diuretics, β blockers, calcium antagonists, ACE inhibitors, and ARBs are considered initial agents in the treatment of hypertension. Thus, this review will focus on the effects of these drug classes on erectile function.

ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin II is known to play a significant role in the pathogenesis of erectile dysfunction. Angiotensin II injected intracavernously terminates spontaneous erection, while the intracavernosal injection of losartan has the opposite effect.[8] Recent animal data indicate that ARBs exert beneficial effects on penile ultrastructure affected by high blood pressure.[9] Several clinical studies support the positive effects of ARBs on sexual function in hypertensive patients.[10–14]

In a study of 82 hypertensive patients with erectile dysfunction (while on various antihypertensive drugs), losartan resulted in a marked increase of self-reported sexual satisfaction.[10] A randomized, double-blind, crossover study comparing valsartan and carvedilol in 160 previously untreated hypertensive patients without erectile dysfunction showed that valsartan (as opposed to carvedilol) significantly improved sexual activity,[11] while in another double-blind, randomized study of 110 previously untreated hypertensive patients, valsartan (as opposed to atenolol) increased sexual activity (although nonsignificantly).[12] These rather small studies, although carefully designed, have some limitations because they used either nonvalidated questionnaires that lacked cutoff scores for erectile dysfunction determination or measured only the number of sexual intercourse events, thus providing quantitative and not qualitative data.

Two large studies have confirmed the beneficial effects of ARBs on sexual function. Della Chiesa and colleagues[13] studied 2202 hypertensive patients and reported an increase of sexual intercourse per week with valsartan. In an even larger study of 3502 hypertensive patients (either on treatment or untreated), valsartan was found to improve all aspects of sexual function and, particularly, erectile function.[14] However, both studies are limited by their open design and either the absence of a control group (only 27 patients in the Della Chiesa study and no control group in the other) or bias in population selection (75.4% patients with erectile dysfunction in the second study). Thus, although available data indicate that ARBs may benefit erectile function, large randomized studies are needed to confirm these findings.

ACE INHIBITORS

ACE inhibitors, apart from reducing angiotensin II production, attenuate the degradation of bradykinin, which is known to activate nitric oxide release and results in subsequent corpus cavernosum relaxation.[15] Experimental data indicate that captopril improves the erectile function of hypertensive rats.[16] Thus, ACE inhibitors are expected to be beneficial on erectile function, based on their effects on the pathobiologic process of erectile dysfunction.

In a double-blind, randomized, crossover study of 90 previously untreated hypertensives, lisinopril had no significant effect while atenolol had negative effects on sexual activity.[17] Another double-blind comparative study of 451 patients reported no difference regarding sexual function between enalapril and amlodipine.[18]

Twenty years ago, Croog and associates[19] examined the quality of life of patients on antihypertensive therapy and reported that patients taking captopril had less sexual dysfunction than those taking propranolol and methyldopa. In a telephone-based study of 134 hypertensive patients, lisinopril had neutral effects on sexual interest, erectile function, orgasmic ability, and satisfaction.[20] Suzuki and colleagues[21] studied 156 hypertensive men and reported that captopril may have advantages over a thiazide diuretic, atenolol, and nifedipine in terms of quality of sexual life, while atenolol resulted in sexual dysfunction and reduced testosterone levels.

It can be stated that, although available data are not quantitatively and qualitatively adequate, ACE inhibitors have neutral effects on erectile function in hypertensive patients. This statement, if confirmed by appropriate studies, suggests that ACE inhibitors are inferior to ARBs with respect to erectile function, possibly due to incomplete blockade of angiotensin II production.

CALCIUM ANTAGONISTS

Existing data regarding the effect of calcium antagonists on erectile function are far from conclusive. Experimental data indicate that calcium antagonists do not exert the beneficial effects of ARBs on penile structure.[22]

Kroner and colleagues[20] studied 134 hypertensive patients and reported that nifedipine and diltiazem showed a trend toward improved sexual function; verapamil, lisinopril, and furosemide had no effect

on sexual function; and hydrochlorothiazide was associated with decreased orgasmic ability. In a 1-year study of 156 hypertensive men, nifedipine exhibited neutral effects on sexual function and testosterone levels.[21] As discussed above, sexual function was not different in hypertensive patients treated with either amlodipine or enalapril.[18] Available data are not adequate to draw definite conclusions; however, they point to a neutral effect of calcium antagonists associated with erectile function.

BETA BLOCKERS

Traditionally, β blockers have been considered a major cause of erectile dysfunction. Previous studies indicate that erectile dysfunction is dose-dependent and more prevalent with older-generation β blockers (propranolol) than with newer ones (celiprolol and carvedilol), with atenolol standing in between.[23–27]

Although evidence seems striking, several methodologic problems are worthy of discussion. For example, in the Medical Research Council (MRC) treatment trial,[23] the incidence of withdrawal due to impotence was significantly higher with β blockers (propranolol) than with placebo ($p<0.001$). However, impotence was found in 13.2% of patients on propranolol compared with 10.1% in the placebo group, and the difference was not statistically significant. Because this was a single-blind study, doctors could have stopped active treatment more easily than the placebo; this could have accounted for the difference between the reported rate of impotence as an adverse event and the withdrawal rate due to impotence. Ko and associates[28] reviewed all available data and reported that β blockers are associated with increased risk of sexual dysfunction (of borderline statistical significance) and impotence; in addition, a significant annual increase of five reports of sexual dysfunction per 1000 patients was found. However, methods assessing impotence in these studies were not of adequate quality according to current standards.

More recent randomized, double-blind studies have confirmed the negative effects of β blockers on sexual function. Atenolol significantly reduced the number of intercourse events per month from 7.8 to 4.2 ($p<0.01$ compared with pretreatment and placebo) in one study[17] and from 6.0 to 4.2 ($p<0.01$) in another study.[12] Similar results were obtained with carvedilol, and sexual intercourse episodes per month were reduced from 8.2 to 3.7 ($p<0.01$ compared with baseline).[11]

On the contrary, preliminary results indicate that nebivolol may exert beneficial effects on erectile function. We studied 44 hypertensive patients while on β-blocker monotherapy. We found that the substitution of β blockers with nebivolol resulted in significant improvement in erectile function in these patients.[29] However, the number of patients is not adequate for definite conclusions, and no placebo arm was included.

The significance of the placebo effect has recently been emphasized by an Italian study of 96 hypertensive patients.[30] Patients were divided into three groups: in the first group, patients were not aware of the type of drug given; in the second group, patients were told that they were taking a β blocker; and in the third group, patients were informed about the drug and its possible adverse effects on erectile function. Erectile dysfunction was 10-fold higher in the third group (31.2%) compared with the first (3.1%), with the second group in between the two others.

DIURETICS

Thiazide diuretics have been the most implicated class of antihypertensives with respect to erectile function. More than 30 years ago, Bulpitt and Dollery[31] drew the attention of the scientific community to the negative effects of antihypertensives regarding erectile function. The MRC trial reported that the incidence of patient withdrawal from the study due to impotence was more than double with diuretics compared with β blockers and several-fold higher than with placebo.[23] However, the methodologic considerations have already been discussed. Thiazide diuretics exert negative effects on sexual function even when used as adjunct therapy. Williams and colleagues[32] reported that patients who had a diuretic added to their therapy experienced sexual dysfunction and a worsening of general well-being, especially in the captopril- and propranolol-treated groups.

Two rather large randomized studies conducted in the United States confirmed the negative effects of diuretics on erectile function. In the Trial of Antihypertensive Interventions and Management (TAIM) study,[7] erection-related problems worsened in 28% of men receiving chlorthalidone, compared with 11% of those receiving atenolol and 3% of those receiving placebo ($p<0.009$). Of interest is the fact that weight reduction ameliorated the negative effect of chlorthalidone on sexual function. In the Treatment of Mild Hypertension Study (TOMHS),[33] participants randomized to chlorthalidone reported a significantly higher incidence of erection problems at 2 years than participants randomized to placebo (17.1% vs. 8.1%; $p=0.025$). However, the difference

between the two groups was not statistically significant at 4 years (chlorthalidone 18.3% and placebo 16.7%). Acebutolol, amlodipine, and enalapril exhibited effects similar to placebo, while doxazosin affected erectile function positively (both in patients with and without sexual problems at baseline). In contrast with the TAIM results, wight loss did not ameliorate the negative effect of chlorthalidone on sexual function.

In the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) study,[34] on the other hand, use of hydrochlorothiazide resulted in no difference compared with candesartan with regard to sex life satisfaction.

Although we have to keep in mind that all of these studies were inadequately assessing erectile dysfunction, without specifically and extensively addressing this issue, the vast majority of available data points to a negative effect of diuretics on erectile function.

SEXUAL DYSFUNCTION AND CARDIAC RISK IN HYPERTENSIVE PATIENTS

According to management recommendations of the Second Princeton Consensus Conference[35] regarding sexual dysfunction and cardiac risk:

- Persons with controlled hypertension are considered low-risk patients and may safely receive approved medical therapies for sexual dysfunction.
- Beta blockers and thiazide diuretics may predispose men to erectile dysfunction.
- There is little objective clinical evidence that blood pressure control will reverse erectile dysfunction.
- A change in class of antihypertensive medication rarely results in the restoration of sexual function.
- Patients with untreated, poorly controlled, accelerated, or malignant hypertension are considered high-risk patients, and sexual activity should be deferred until the patient's condition has been stabilized by treatment or a decision has been made by a cardiologist and/or internist that sexual activity may be safely resumed.

Although scientific data support the first three statements, the fourth and fifth merit discussion. Regarding the fourth statement, Dusing[14] studied the effects of valsartan on erectile function in patients taking (n=2550) or not taking (n=952) antihypertensive therapy. He reported that men with erectile dysfunction while on various antihypertensive drugs exhibit a marked improvement of erectile function when treated with valsartan. Although the study is limited by its open design and the absence of a placebo arm, it represents the conditions found in everyday clinical practice. Thus, unless other studies challenge the beneficial effect of ARBs on erectile function, we believe that current data support a switch to ARBs as a useful measure for hypertensive men with erectile dysfunction while on other antihypertensive agents, before selecting a PDE-5 inhibitor for the management of erectile dysfunction. However, if the treating physician chooses to continue current antihypertensive treatment, PDE-5 inhibitors may be added to therapy.

Although available data support most of the fifth statement, the first part needs clarification (i.e., untreated hypertensive patients are at high risk and sexual activity should be deferred). We believe that patients with mild hypertension are not included in this group; although it is appropriate for such patients to visit a cardiologist and/or internist for blood pressure control, sexual activity should not be deferred since the absolute cardiac risk during sexual activity is considerably low even in patients with documented heart disease. Low-risk patients have a cardiac event risk rate of one in one million, with sexual activity increasing this risk to two in a million during the 2-hour post-intercourse period (through activation of the sympathetic system, resulting in heart rate and blood pressure increases). Although patients with coronary heart disease have a 10-fold increased risk, the absolute risk remains considerably low (20 per million).

PDE-5 INHIBITORS IN PATIENTS WITH HYPERTENSION

The statement of the American College of Cardiology/American Heart Association (ACC/AHA) published in 1999 regarding sildenafil use in patients with cardiovascular disease seems partly outdated, since the fear of potential consequences was due to the absence of data at that time.[36] Concerns had been raised regarding sildenafil use in patients taking complicated, multidrug, antihypertensive regimens, where sildenafil could be "potentially hazardous." At that time, most patients in randomized studies that evaluated sildenafil use were controlled with one antihypertensive agent, and only a small number were controlled with three antihypertensive agents. Thus, the ACC/AHA committee concluded that sildenafil should be prescribed with caution in such patients until appropriate studies were performed. Current available data strongly indicate that PDE-5 inhibitors may be safely coadministered with all classes of antihypertensive drugs (caution with α blockers), even in patients taking multiple antihypertensive

agents.[37–39] Thus, we believe that the time has come for minor revisions regarding these issues.

According to the 2005 American Urological Association guidelines regarding the use of PDE-5 inhibitors with α blockers, vardenafil is contraindicated, while tadalafil and sildenafil (at 50 mg and 100 mg) should be administered with caution in all patients taking α blockers.[40] According to the new labeling, α blockers are no longer considered a contraindication for all three PDE-5 inhibitors, but precautions are listed.

We must not forget that some β blockers possess α-blocker activity as well (labetalol, carvedilol); thus, PDE-5 inhibitors should be used with caution until appropriate data become available.

CONCLUSIONS AND FUTURE PERSPECTIVES

Older-generation antihypertensive drugs (central-acting, β blockers, diuretics) negatively affect erectile function, while newer-generation agents (calcium antagonists and ACE inhibitors) seem to have neutral effects, and ARBs exhibit a beneficial effect on erectile function (Table). However, available data cannot be characterized as of high quality since they are mostly derived either from open studies or by using inappropriate assessment methods. Thus, accurate studies (double-blind, using appropriate inventories) are needed to clarify these unresolved issues.

In the case of erectile dysfunction resulting from antihypertensive drugs, the physician may either add PDE-5 inhibitors or substitute current treatment with drugs with a better profile regarding sexual side effects (ARBs); if erectile dysfunction persists, the treating physician may add PDE-5 inhibitors to relieve symptoms, improve quality of life and, more importantly, ensure adherence to antihypertensive treatment (Figure).

Erectile dysfunction represents a patient-driven field at this time, with the basic component being the patient's curiosity to understand and find relief of his symptoms. Most of the time health care professionals respond to patients rather inadequately, possibly because the extent of this problem is not appreciated and knowledge of the underlying pathophysiology and current treatment options is still poor. Thus, general practitioners, internists, cardiologists, nephrologists, and other hypertension specialists need to be appropriately educated in recognizing and managing erectile dysfunction in patients. Physicians are reluctant to incorporate sexual health into their practice, partly due to a lack of familiarity with the subject and partly due to time constraints. Thus, we believe that appropriate education of physicians and nurses is urgently needed to overcome this issue.

Table. The Effect of Antihypertensive Drug Classes on Erectile Function

Antihypertensive Drugs	Effect on Erectile Function
Central-acting	– – –
Diuretics	– –
β Blockers	–
Calcium antagonists	±
Angiotensin-converting enzyme inhibitors	±
α Blockers	+
Angiotensin receptor blockers	+

–=negative effect; ±=neutral effect; +=positive effect

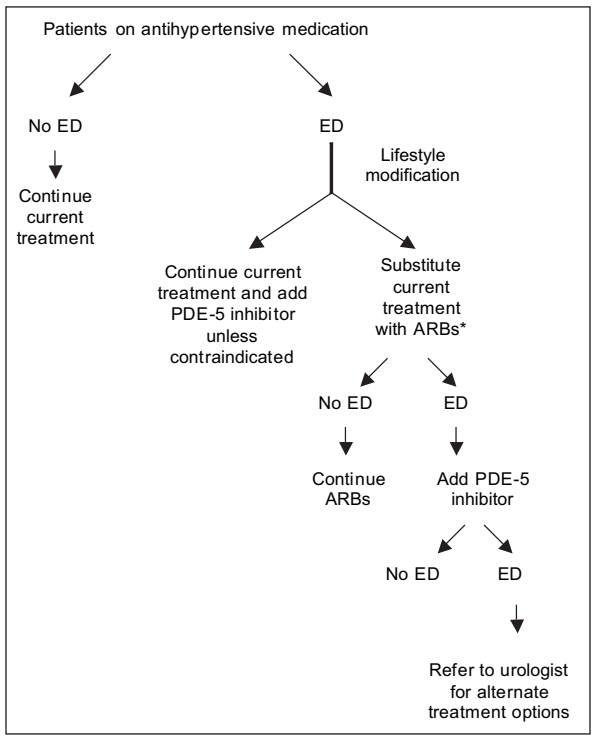

*Figure. Proposed algorithm for the management of erectile dysfunction (ED) in hypertensive patients who take antihypertensive drugs. PDE-5=phosphodiesterase-5; ARBs=angiotensin receptor blockers; *unless contraindicated and/or current treatment is absolutely indicated*

Finally, erectile dysfunction should be considered an early sign of vascular disease (even the earliest window) and ought to be the subject of extensive inquiry in all patients with essential hypertension.

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